New Drugs for Bad Bugs

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Disclosures

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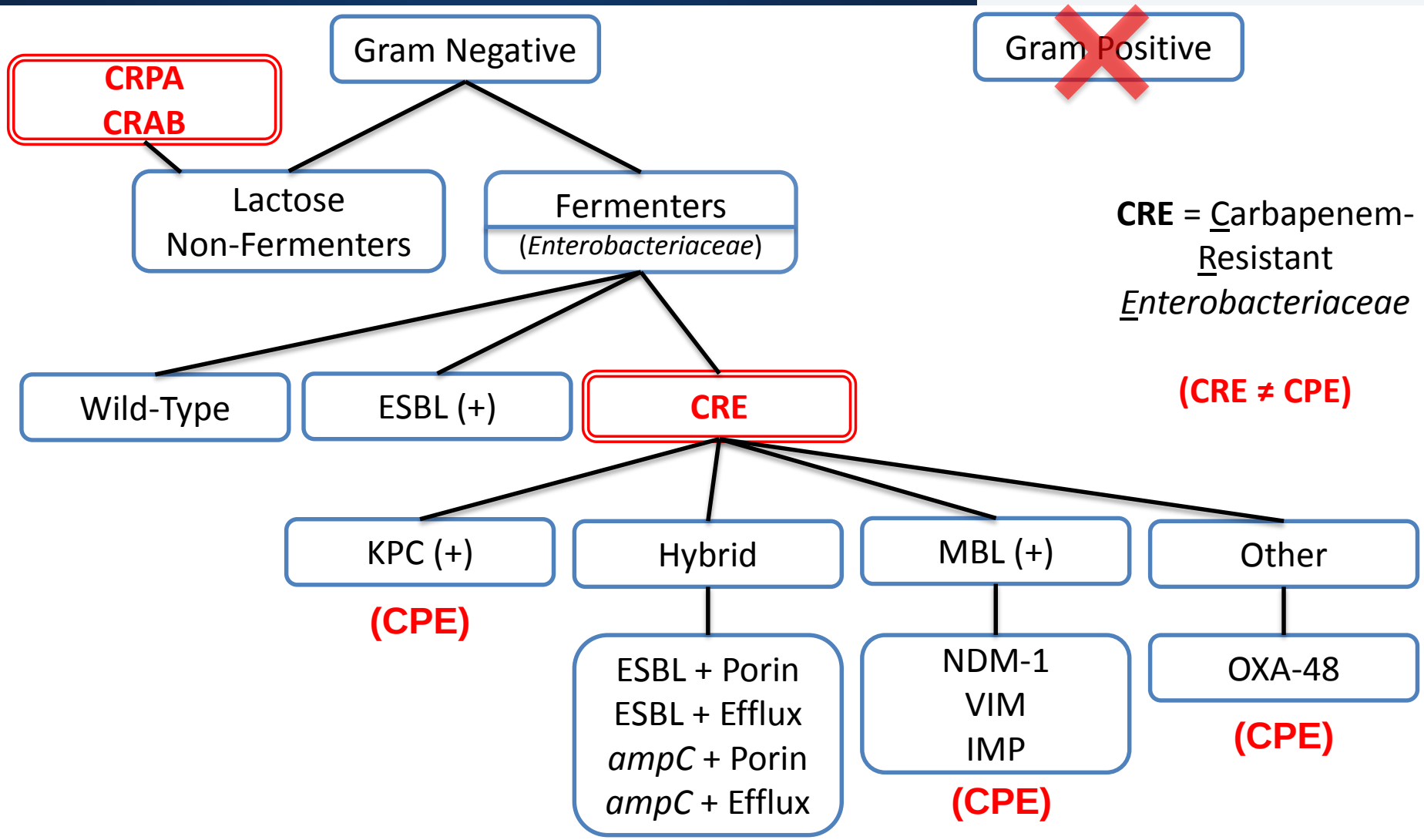
- I have no financial or personal disclosures relevant to this presentation.

- I will be discussing some non-FDA-approved use of antimicrobials as well as un-approved antimicrobials.

Objectives

- Recall resistance patterns for ICU-acquired infections
- Review recently approved antibiotics available for treatment of multi-drug resistant infections

"What's in a name…"



CRE = Carbapenem-Resistant *Enterobacteriaceae*

(CRE ≠ CPE)

ESBL = extended-spectrum betalactamase, KPC = Klebsiella pneumonia carbapenemase,
MBL = metallobetalactamase, NDM = New Delhi metalobetalactamase, CPE = carbapenemase producing Enterobacteriaceae,
CRPA = carbapenem R P.aeruginosa, CRAB = carbapenem R Acinetobacter

Ceftolozane/Tazobactam
(Zerbaxa™)

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Unmet Need: MDR Pseudomonas

- May have utility in CPE(-) CRE infections
  - Debate over BLI's in ESBL(+) infections
  - MERINO study (poor outcomes for Pip/Tazo)
  - ESBLs were included in Phase-III studies
- Typically gains 2-3 tube dilutions (MIC) better than Cefepime/Ceftazidime
- Remember metronidazole when indicated
- 1.5gm dose = 1gm Ceftolozane/0.5gm Tazobactam

BLI = betalactamase inhibitor, MOSAIC - *JAMA*. 2018;320(10):984-994, *Clin Infect Dis*. 2015;60(10):1462-71

Ceftazidime/Avibactam
(Avycaz™)

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Unmet Need: CRE

- Avibactam – novel non-betalactam BLI that regenerates upon hydrolysis (re-usable)
- Inhibits ESBL, KPC, ampC and OXA-48
- FDA – cUTI and cIAI
- Remember metronidazole
- 2-hour infusion
- Resistance is already well characterized (D179Y mutation in the KPC enzyme)

cUTI = complicated urinary tract infection, cIAI = complicated intra-abdominal infection

Meropenem/Vaborbactam
(Vabomere™)

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Unmet Need: CRE

- Vaborbactam = novel cyclic boronic acid BLI
- Inhibits ESBL, KPC, ampC (not OXA-48)
- FDA – cUTI
  - Novel approval path: 1 RCT, 1 pathogen directed trial
    - TANGO-I (cUTI vs. pip/tazo)
    - TANGO-II (CRE, any source vs. BAT – including BSI, HAP/VAP, cIAI, cUTI)
  - TANGO-II included both immunocompromised patients and Ceftaz/Avi treated patients
  - 3-hour infusions & 4-hour stability
  - QIDP status from FDA

TANGO-II - *Infect Dis Ther*. 2018 Oct 1 (epub), BSI = blood stream infection, QIDP = qualified infectious diseases product (GAIN Act)

Plazomicin
(Zemdri™ - June 2018)

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Unmet Need: MDR GNRs

- Aminoglycoside ("neoglycoside")
- FDA – GNR cUTI (denied BSI indication)
- Synergistic activity vs. both Gm(-) and Gm(+)
- More potent than current AGs
- ODA dosing (requiring dose-reduction and TDM if CrCl < 90 ml/min)
- Same ADR profile as current AGs
- Formulary approval = a new drug & a new lab

ODA – once daily aminoglycoside, TDM = therapeutic drug monitoring, AG = aminoglycoside

Eravacycline
(Xerava™ - August 2018)

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Unmet Need: CRAB, maybe CRE

- "Novel" flurocycline (Similar to Tigecycline)
  - Broad Gm(+), Gm(-) and anaerobe spectrum
  - No activity against Pseudomonas
- FDA – cIAI
  - Failed cUTI vs. Levofloxacin
  - cUTI likely to follow pending additional Phase-III with augmented oral dose and sNDA
- IV (with PO likely to follow post redesigned Phase-III UTI)
- Typical TCN ADEs – photo-, HA, GI (less than Tiga)
- The future… STIs (Gonococcus) and NTM?

STI = sexually transmitted infection, NTM = non-tuberculous mycobacteria

Omadacycline
(Nuzyra™ - October 2018)

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Unmet Need: CRAB, maybe CRE

- Tetracycline
  - Empty stomach, no dairy, multi-valent cations
  - Teeth and bones
  - Typical TCN ADEs – photo-, HA, GI (less than Tiga)
- FDA – CABP and ABSSSI (maybe UTI to follow)
- IV and PO, once daily dosing
- Despite FDA filing, still with activity against MDR Gm(-)s and Gm(+)s (not Pseudomonas)
- QIDP status
- The future… STIs (Gonococcus) and NTM?

CABP = community-acquired bacterial pneumonia, ABSSSI = acute bacterial skin/soft-tissue infection

Notable Pipeline Agents

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Cefiderocol
(S-649266)

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Unmet Need: CRPA, CRAB, likely CRE (hybrids)

- Novel siderophore cephalosporin
  - MOA is typical of betalactam
  - Entry into bacterial cell is via iron transporters
  - More potent than current carbapenems
- Stable against ESBL and MBLs, but higher MICs against KPC-2 (breakpoints pending)
- First half of 2019
- QIDP status

Imipenem/Cilastatin/Relabactam

(MK-7655A)

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Unmet Need: CRE

- Comparable to Mero/Vaobor
- Similar regulatory track to Mero/Vabor (pathogen driven + HAP/VAP)
- QIDP status
- Phase-III, pending NDA submission
- Likely 2019

IV Fosfomycin
(Contempo™)

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Unmet Need: CRE, MDR Gram Positive

- Wealth of data from the EU
- Positive experience in the US with MDR UTIs
- Broad Gm(+) and Gm(+) activity (+/- Pseudomonas)
- Phase-III for UTI/Pyelonephritis pending
- NDA filing likely in 2019

Reflections

- Formulary – Ceftaz/Avi vs. Mero/Vabor (vs. Imi/Rel) – either, neither or both?
- New Tetracyclines vs. Tigacycline (vs. Mino)?
- Do you need another Aminoglycoside? (TDM)
- Cefiderocol – Are you a CF and/or Lung SOT center?
- Betalactam sparing strategies?

Pogue JM. *Clin Infect Dis*. 2018: Jul 18

Learning Assessment
#1

Resistance in contemporary MDROs is mono-modal (ie, a single novel beta-lactamase)?

a) True
b) False

FALSE - While novel beta-lactamases exist and are epidemiologic threats, multi-modal resistance (beta-lactamase plus efflux/porin) plays a significant role.

Learning Assessment
#2

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Which of the two recently FDA approved novel agents occupy the same functional space in our antimicrobial armamentarium?

a) Ceftolozane/Tazobactam and Meropenem/Vaborbactam
b) Ceftolozane/Tazobactam and Ceftazidime/Avibactam
c) Meropenem/Vaborbactam and Ceftazidime/Avibactam

C) these agents are our two primary tools against KPC-producing CREs.


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